REMARKS

Claims 2-38 are pending. Claim 1 was cancelled in applicants' last response, and applicants have amended claim 27 to correct a spelling error in the last response. Applicants have amended claim 33 to remove a duplicate word. These amendments add no new matter.

35 U.S.C. § 103

Claims 2-38 have been rejected as being allegedly unpatentable over Xu et al. (U.S. 2003/0104432 A1; "Xu") in view of Godfrey et al. (U.S. Patent No. 7,101,663; "Godfrey"). Applicants traverse this rejection for the following reasons.

According to the Office Action at page 3,

> Xu et al. teach a method of claim 2, 9-10, 20, 28-29, 38, for producing amplified RNA (aRNA) comprising
>
> (a) reverse transcribing an RNA template using a promoter-primer complex and an RA dependent DNA polymerase (reverse transcriptase enzyme) to produce a first strand cDNA (see page 5, paragraph 0073-0079, page 7, paragraph 0092);
>
> (b) treating the reverse transcription product with RNAse H enzymatic activity (see page 7, paragraph 0093);
>
> (c) producing a second strand cDNA complementary to said first strand cDNA using a DNA dependent polymerase, **in the presence of random primers to prime the synthesis of said second strand cDNA** (see page 7, paragraph 0094-0095, page 9, paragraph 0119-0123);
>
> (d) producing amplified RNA from the eluted double stranded cDNA by in vitro transcription using a DNA dependent RNA polymerase which initiates transcription from the promoter-primer complex (see page 8, paragraph 0101, page 9, paragraph 0124-01125);
>
> wherein the product produced after c), after d) or both is purified by contacting said product with a solid phase which binds nucleic acids followed by eluting bound nucleic acids from the solid phase dissolved in less than 50 ul (see page 9, paragraph 0125, page 11, claims 9-11, page 9, paragraph 0134)(bold emphasis added).

Applicants respectfully disagree with a key incorrect presumption by the Office. As highlighted in the passage quoted above, the Office Action simply asserts that Xu describes preparing the second strand cDNA using random primers to prime the synthesis of the second strand cDNA, and cites page 7, paragraph 0094-0095, and page 9, paragraph 0119-0123 of Xu as the alleged support for this assertion. Applicants have carefully reviewed Xu, and cannot find any evidence that Xu describes the use of **random primers** to prime the synthesis of the **second strand of cDNA**. Xu at page 7, paragraphs 0094 and 0095 mentions the use of random primers, but only with respect to priming the **first** strand of cDNA. This is also clear from FIG. 7, which is described in paragraph 0095. When one turns to page 9, paragraphs 0119-0123, also cited in the Office Action, it is clear that here Xu is describing "First Strand cDNA Synthesis" (see subheading at paragraph 0122). More importantly, there is no mention whatsoever of "random primers" in any of paragraphs 0119-0123. Thus, again, there is no discussion of random primers used to prime the synthesis of the **second** strand of cDNA.

This is a clear distinction between the presently claimed invention and the cited prior art, in which primers containing a known sequence are used to prime the synthesis of the second strand of cDNA, and random primers are used, if at all, only for priming synthesis of the first stand of cDNA. Random primers can maximize the reliability of the amplification reaction, minimize reaction times, and provide greater uniformity in the length of the amplified antisense RNA product.

The Office also concedes (at page 4 of the Action) that, "Xu et al. did not specifically teach completion of first and second cDNA synthesis in less than 45 minutes" (at page 4), but alleges that, "Godfrey et al. teach rapid RT-PCR method which is performed in less than 10 minutes (see col. 2, line 62-67, col. 3, line 1-3)" (id.). The Office then concludes (at page 4):

> it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of producing aRNA as taught by Xu et al. with a step of completing the reaction in less than 45 minutes as taught by Godfrey et al. to achieve [the] expected advantage of developing a sensitive and enhanced method of producing aRNA. An ordinary practitioner would have been motivated to combine the teaching of Xu et al. with the step of completing the reaction in less time as taught by Godfrey et al. because one skilled in the art would have a reasonable expectation of success that the

> combination would result in a rapid, automated method for RT-PCR (see col. 2, line 62-67, col. 3, line 1-3) and such modification of the method would be considered as obvious over cited prior art " (Office Action at page 5).

Applicants respectfully disagree. First, as noted above, Xu fails to recite the use of random primers to prime the synthesis of the second strand of cDNA. Godfrey does not remedy this clear shortcoming of Xu. In fact, applicants have carefully searched Godfrey, and the only reference to the use of a random primer is in Example 1, in a test of the effect of a wax layer on the ability of the system to detect fluorescence (see column 16, lines 46-55). This description is totally irrelevant to an analysis of obviousness of the present claims.

Second, Godfrey clearly states that "the specificity of any given PCR reaction relies heavily, but not exclusively, on the identity of the primer sets" (column 6, lines 7-8). Godfrey also describes the use of high concentrations of "PCR primer sets specific to the cDNA" and "PCR-optimized primers" (at column 6, lines 58-59 and 65). Similarly, in the Examples, Godfrey notes the use of specific primers, such as CEA primers used in Example 4 that were designed to span a junction between specific exons of CEA mRNA. Thus, one of skill in the field making the combination of Xu and Godfrey as the Examiner alleges would never have thought to use random primers to prepare the second strand of cDNA as presently claimed.

Thus, applicants submit that the Office has failed to establish a *prima facie* case of obviousness, as none of the references, or any combination thereof, would provide the claimed invention. As a result, claim 1 is clearly patentable.

The Office Action also makes various statements about the dependent claims. Applicants will address some of these claims below.

With regard to claims 7, 8, 23, and 24, the Office Action (at page 4) alleges that Xu describes that the random primers have six to 10 nucleotides (citing page 3, paragraph 0042, page 11, and claim 17). Applicants reiterate that the random primers described here relate to first strand cDNA synthesis, and thus are not relevant to the presently claimed invention.

With regard to claims 12-19 and 30-37, the Office Action (at page 4) alleges that Xu describes the use of "magnetic beads or silica particles to purify the first or the second cDNA

product, said purification involves centrifugation at high speed without the use of a vacuum (see page 9, paragraph 0125, 0134, microcon-30 filter device)." Applicants respectfully disagree with this assertion. What Xu describes at page 9 in these paragraphs is the use of a Millipore Microcon-30® centrifugal filter device. According to the Millipore website, this device contains a filter membrane made of regenerated cellulose and not silica. In fact, applicants could not find the term "silica" anywhere in Xu. While Xu does mention the use of magnetic beads, applicants are not claiming the use of magnetic beads. Thus, applicants submit that claims 12-19 and 30-37 are patentable for this additional reason as well.

Given a careful analysis of the cited prior art, it is clear that the cited prior art does not disclose one of the elements of claim 1, the use of random primers for the synthesis of the second strand of cDNA, and in fact, Godfrey teaches away from the use of random primers. Thus, applicants submit that the Office has failed to establish a *prima facie* case of obviousness for claim 1, and all of the remaining dependent claims 2 to 38 as well. As a result, applicants request that the Examiner reconsider and withdraw the rejection of claims 2 to 38.

CONCLUSION

Applicants submit that the all of the claims are in condition for allowance and request entry of the proposed amendments and confirmation of allowance by the Examiner. It is believed that all of the pending issues have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify applicants' agreement. In addition, because the arguments made above may not be exhaustive, there may be additional reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Further, the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants have enclosed a $490 check for an extension fee along with a Petition for an Extension of Time of Two Months. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14255-0052US1.

Respectfully submitted,

Date: 6/8/09

FOR J. Peter Fasse
Reg. No. 32,983

Reg. No. 54,112

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22186534.doc